D = dose
$D_B = X_B + (1 - F_{G1})D$
$D_T = F_{G1}D + F_BD_B$, the apparent amount of the dose absorbed
F = AUC_{po}/AUC_{iv}, the apparent fraction of the dose absorbed
F_B = fraction of drug accumulated in B that is released to G at time $t = t_B$
F_{G1} = fraction of D absorbed by first-order absorption into the central compartment
$1 - F_{G1}$ = fraction of D transferred from G to B
G = compartment from which absorption takes place
K_{ZZ} = first-order transfer rate constants
t = time
t_L = lag time
t_B = time when a part (F_BD_B) of the drug accumulated in B is released to G
Vd = volume of distribution
X_B = amount of drug transferred from compartment 1 to compartment B at time $t = t_B$

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Dose-Dependent Pharmacokinetic Study of Pefloxacin, A New Antibacterial Agent, in Humans

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Received June 29, 1983 from the *Laboratoire de Biochimie I et de Pharmacologie, Centre Hospitalier Intercommunal de Créteil, 94010 Créteil Cedex, France.* Accepted for publication September 26, 1983.

Abstract □ A dose-dependent pharmacokinetic study of pefloxacin was performed after four intravenous infusions and four orally administered doses. After intravenous infusion, the pharmacokinetic profiles of the plasma concentrations showed a biphasic decline, with half-lives (mean ± *SD*) of 8.55 ± 4.20 min and 11.50 ± 1.75 h, respectively. Intravenous infusion and oral administration yielded similar results. The pharmacokinetic parameters remained constant in the dose range of 200–800 mg from the plasma and urine data.

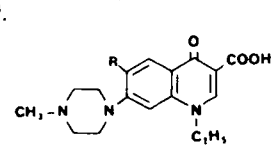
Keyphrases □ Pharmacokinetics—dose-dependent, pefloxacin, new antibacterial agent □ Pefloxacin—new antibacterial agent, dose-dependent pharmacokinetics □ Antibacterial agent—dose-dependent pharmacokinetics of pefloxacin

Pefloxacin[1], 1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid (I), is a new antibacterial compound shown to be highly active against both Gram-negative and Gram-positive bacteria (1, 2). A large percentage (85%) of the drug administered is transformed into several metabolites, the *N*-oxide, the demethyl, and the oxodemethyl analogues (3). Since the pharmacokinetic data for this drug have not been reported in humans, a preliminary study was performed to investigate the plasma and urine profiles of pefloxacin in a dose-dependency study in humans.

EXPERIMENTAL SECTION

Materials—Pefloxacin and its 6-chloro analogue[1] (II) (the internal standard) showed no impurities in two different TLC systems. All reagents were commercially available analytical grades and used without further purification.

Pefloxacin Analysis—Unchanged pefloxacin in plasma or urine was measured by HPLC (3) using a liquid chromatograph[2] equipped with a UV spectrophotometer (280 nm) and a continuous flow cell with an 8-μL capacity. A 200-mm steel column was used, packed with a monomolecular layer of octadecyltrichlorosilane chemically bonded to silica beads with an average particle size of 7 μm[3].



I: R = F
II: R = Cl

[1] Roger Bellon Laboratories, Alfortville, France.

[2] Waters Associates, Paris, France.

[3] Lichrosorb RP-18; Merck, Paris, France.

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Table I—Pharmacokinetic Parameters (Mean ± *SD*) Obtained after Intravenous Infusion of Pefloxacin

Parameter	Dose, mg			
	200	400	600	800
$t_{\alpha,1/2}$, h	0.10 ± 0.05	0.13 ± 0.06	0.09 ± 0.03	0.25 ± 0.07
$t_{\beta,1/2}$, h	9.7 ± 2.1	10.7 ± 1.4	11.8 ± 2.3	13.8 ± 2.7
k_{13}, h^{-1}	0.686 ± 0.675	0.160 ± 0.030	0.170 ± 0.125	0.130 ± 0.064
k_{12}, h^{-1}	7.35 ± 5.54	3.46 ± 1.55	5.63 ± 2.66	3.087 ± 3.582
k_{21}, h^{-1}	1.149 ± 0.094	2.422 ± 0.861	2.12 ± 0.27	1.661 ± 0.709
Vd_1, L	23.2 ± 19.1	46.9 ± 8.7	68.2 ± 20.0	54.6 ± 21.8
Vd_2, L	100.9 ± 40.9	64.8 ± 4.1	83.5 ± 14.7	65.3 ± 30.9
AUC, mg·h/L	23.4 ± 9.3	54.3 ± 4.1	82.2 ± 22.5	130.9 ± 23.7
CL, mL/min	156.4 ± 53.7	123.1 ± 9.8	27.2 ± 31.0	104.8 ± 19.3
U_∞, mg	27.4 ± 13.1	—	76.2 ± 37.1	84.8 ± 19.3
U_∞, %	13.7 ± 6.5	—	12.5 ± 6.6	10.8 ± 2.1
CL_R, mL/min	19.6 ± 5.6	—	15.2 ± 6.6	12.0 ± 0.3

Table II—Pharmacokinetic Parameters (Mean ± *SD*) Obtained after Oral Administration of Pefloxacin

Parameter	Dose, mg			
	200	400	600	800
Lag time, h	0.32 ± 0.14	0.48 ± 0.23	0.26 ± 0.11	0.28 ± 0.22
k_r, h^{-1}	2.11 ± 0.25	1.59 ± 0.71	2.73 ± 2.12	4.01 ± 2.28
$t_{1/2,r}$, h	0.33 ± 0.04	0.46 ± 0.27	0.35 ± 0.19	0.25 ± 0.20
$t_{1/2,el}$, h	11.7 ± 3.6	10.5 ± 2.0	11.3 ± 1.1	12.6 ± 2.5
Vd, L	132.2 ± 26.9	112.0 ± 20.5	109.9 ± 17.7	137.9 ± 2.1
AUC, mg·h/L	25.7 ± 6.3	54.5 ± 11.2	87.9 ± 8.9	105.0 ± 20.7
CL_T, mL/min	135.3 ± 35.5	125.7 ± 25.7	111.3 ± 7.0	130.6 ± 28.6
U_∞, mg	23.6 ± 8.0	44.3 ± 17.3	84.1 ± 23.5	136.4 ± 26.7
U_∞, %	11.8 ± 4.0	11.1 ± 4.3	14.0 ± 3.9	17.0 ± 3.3
CL_R, mL/min	15.3 ± 3.8	12.9 ± 2.6	14.7 ± 3.6	21.9 ± 4.8

The detection limit of the technique was 0.05 μg/mL in plasma and 0.5 μg/mL in urine, with an overall recovery of 90% from both plasma and urine. Standard curves showed good linearity from 0.125 μg/mL to 10 μg/mL, $r > 0.995$.

Human Experiments—Three subjects gave informed consent to participate in the study. They were found to be free from cardiac, renal, hepatic, respiratory, and allergic diseases by clinical and biological examinations. None of the subjects received any drugs for at least 15 d prior to the study. Each subject received four doses (200, 400, 600, and 800 mg) at weekly intervals both by intravenous infusion over 1 h and orally in 200-mg tablet form. Oral administrations were given after a 15-d wash-out period.

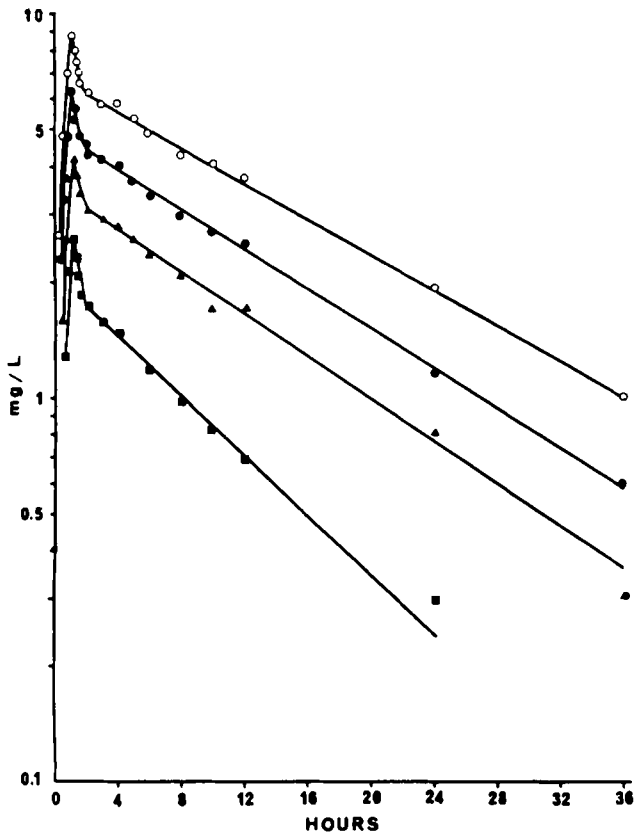

Figure 1—*Plots of mean plasma concentrations of pefloxacin* versus *time obtained in three subjects for each infused dose. The lines were generated from the best-fit pharmacokinetic parameters. Key: (■) 200 mg; (▲) 400 mg; (●) 600 mg; (○) 800 mg.*

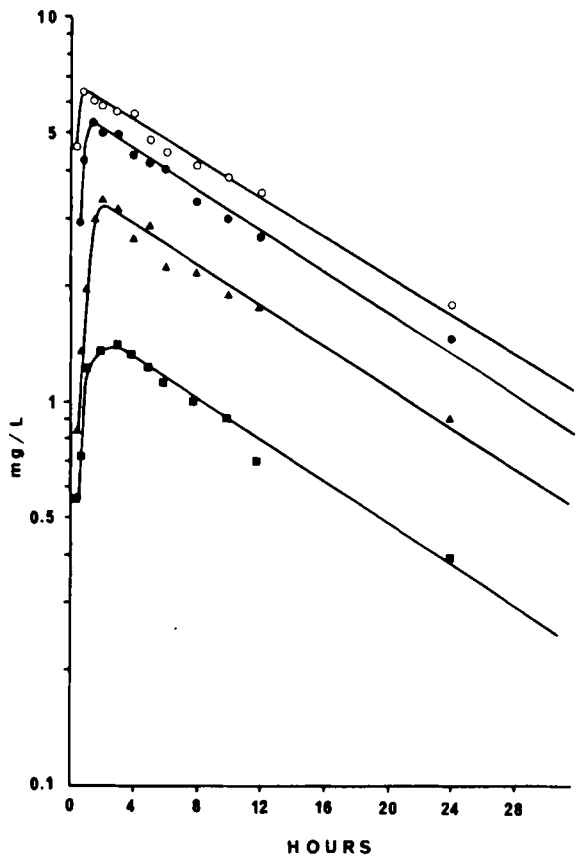

Figure 2—*Plots of mean plasma concentrations of pefloxacin* versus *time obtained in three subjects for each orally administered dose. The lines were generated from the best-fit pharmacokinetic parameters. Key: (■) 200 mg; (▲) 400 mg; (●) 600 mg; (○) 800 mg.*

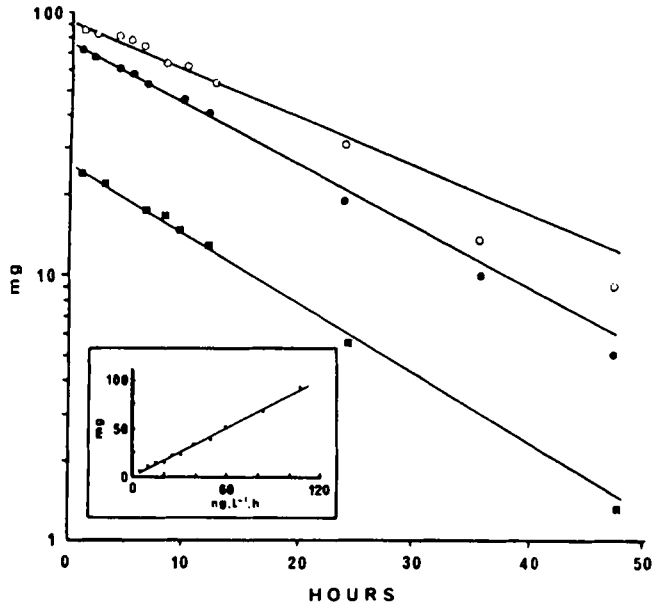

Figure 3—*Semilogarithmic plots of the amounts remaining to be excreted* versus *time in three subjects after an infused dose. Key: (■) 200 mg; (●) 600 mg; (○) 800 mg. Inset: An example of a clearance plot obtained in subject A after an infused dose of 800 mg.*

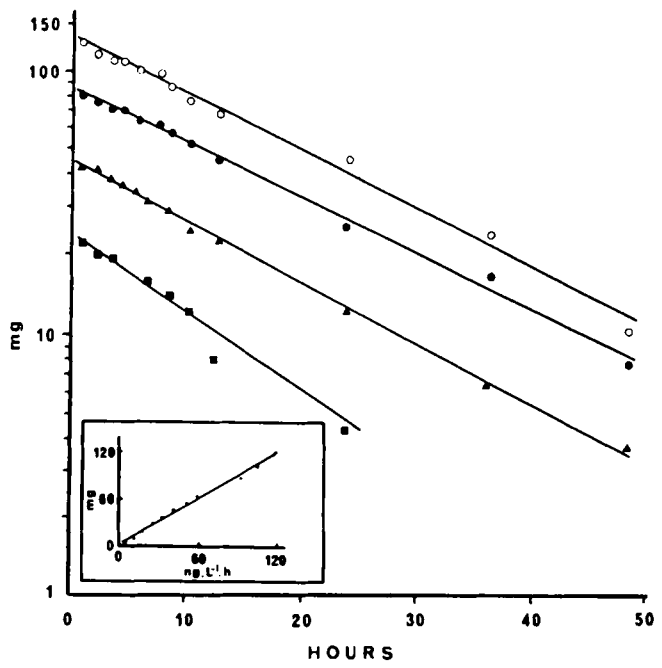

Figure 4—*Semilogarithmic plots of the amounts remaining to be excreted* versus *time in three subjects after an orally administered dose. Key: (■) 200 mg; (▲) 400 mg; (●) 600 mg; (○) 800 mg. Inset: An example of a clearance plot obtained in subject A after the orally administered dose of 800 mg.*

A 7-mL heparinized blood sample was drawn at 0, 0.25, 0.5, 0.75, and 1 h during the infusion and at 10, 15, 30, and 45 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 24, 36, and 48 h after the cessation of the infusion. After oral administration, sampling took place at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, and 38 h. When variations of the infusion period or the sampling times occurred, the actual times were noted.

Urine samples were collected every hour during the first 6 h, every 2 h during the next 6 h, and every 12 h for the next 3 d.

Calculations—Statistical and pharmacokinetic calculations were performed with a table computer[4] using programs developed previously (4).

RESULTS AND DISCUSSION

Blood Sample Analysis—*Intravenous Infusion*—The mean pefloxacin plasma concentrations obtained from the three subjects receiving intravenous doses are shown in Fig. 1. Individual concentrations were systematically interpreted according to three different pharmacokinetic models, *i.e.*, one-, two-, or three-compartment open models using a Gauss–Newton algorithmic method. When pefloxacin was infused, the rate of input of the drug into the compartmental model was treated as a zero-order process; however, it was a one-order process when given orally.

At each step, the benefit of increasing the number of compartments was evaluated with a statistical Fischer test using the least-squares criterion. It showed that the two-compartment open model was the most suitable. The mean pharmacokinetic parameters (mean ± *SD*) are listed in Table I. It shows a rapid distribution phase corresponding to a 0.146 ± 0.04 h half-life (range: 0.084–0.477) and an elimination phase with an 11.5 ± 2.5 h mean half-life (range: 7.3–15.5). The volumes of distribution are large with a mean of 40.1 ± 19.1 L (range: 6.9–66.7 L) for the central compartment and 78.2 ± 28.5 L (range: 46.2–101.0 L) for the peripheral compartment.

Oral Administration—Mean pefloxacin concentrations obtained from the three subjects receiving oral doses are shown in Fig. 2. With this route of administration, the best fit was obtained with the one-compartment open model and first-order absorption. The mean pharmacokinetic parameters are presented in Table II. All parameters are in the same range as those obtained after intravenous infusion. The apparent elimination half-lives and the areas under the plasma concentration curves are essentially identical. From this last observation, it can be stated that the absolute availability of the tablets was complete, in these subjects, at each dose so that apparent volumes of distribution and total elimination clearances need not be corrected after oral administration of the drug. The distribution phase does not appear after oral administration, being masked by the absorption phenomenon from the GI tract.

Urine Sample Analysis—*Intravenous Infusion*—The rate of unchanged pefloxacin elimination was plotted against the plasma concentration at the corresponding mid-point time of urine collection. It showed a roughly linear renal clearance in each subject for all doses administered ($r > 0.85$). If the renal clearance is constant as a function of time and drug concentration, it is then possible to compute concomitantly the plasma concentrations and the rate of urinary elimination according to the general relation:

$$\frac{dU}{dt} = CL_R \cdot C \cdot dt$$

In each case, a single set of exponential terms adequately described both the plasma concentrations and the urinary elimination of the drug ($r > 0.95$ between observed and calculated values). The total amount excreted in the urine and the estimated renal clearance were added up and are presented in Table I. Furthermore, this concomitant analysis of plasma and urine data clearly show that the renal clearance was independent of the plasma drug concentrations. The urinary data, shown in Fig. 3, are plotted as the semilogarithmic amounts remaining to be excreted *versus* time. As one urine sample could not be collected after the intravenous infusion of the 400-mg dose, the corresponding plot was not drawn.

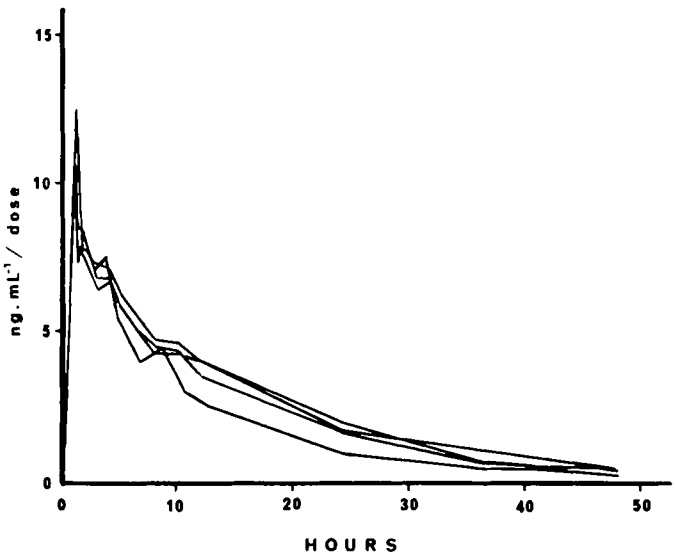

Figure 5—*Superposition of the plasma concentration curve divided by the intravenously administered dose as a function of time, in subject M.*

[4] Model 4052; Tektronix, Paris, France.

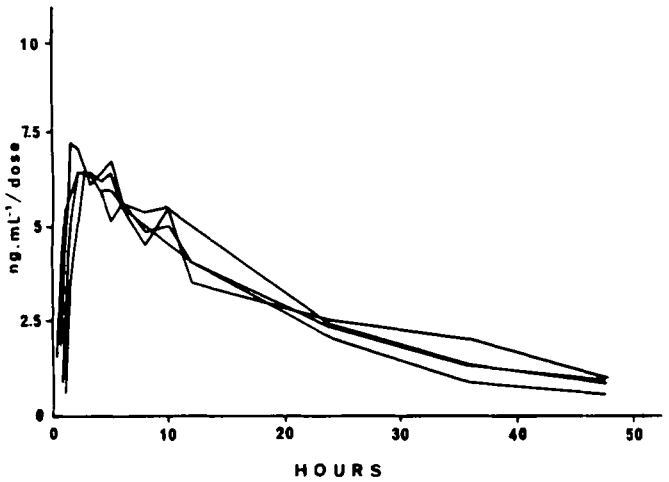

Figure 6—*Superposition of the plasma concentration curve divided by the orally administered dose as a function of time, in subject A.*

The examination of the cumulative excretion curves showed that the time of urinary collection, 4 d, was enough to have a good approximation of the total amount of the drug excreted at infinity. This result was in good accordance with a mean apparent elimination half-life of 12 h. It showed that the urinary excretion of unchanged drug accounted for 14.5 ± 6.5% of the infused drug, which was close to the results obtained in one subject in a preliminary study (3).

Oral Administration—The same pharmacokinetic analysis was performed with the data obtained after oral pefloxacin administration. The urinary data are shown in Fig. 4. The overall recovery of unchanged drug was 13.5 ± 4.1% of administered dose, similar to that observed after intravenous infusion. From this result, a high availability (close to 100% of the dose) could again be expected.

Analysis for Dose-Dependent Kinetics—The phamacokinetic analysis showed that urinary elimination, namely the renal clearance, was independent of the administered dose and plasma concentrations. Since this urinary elimination of the parent drug accounted for only 14.5% of the dose administered, 85.5% of the dose was likely to be eliminated by metabolic routes. Therefore, it was necessary to check the dose independency with parameters which took into account the overall mechanisms of drug elimination. Three methods were used to check the dose dependency from plasma results. Examples of the superposition method are shown in Figs. 5 and 6. The plasma concentrations divided by the administered dose as a function of time show a reasonable superposition for the four doses tested, either after intravenous infusion or oral administration.

According to Dost's law (5), if pharmacokinetic parameters are independent of the dose, the area under the plasma concentration curve must be linearly related to the injected dose. The mean correlation coefficients were 0.956, 0.990, and 0.998 for each subject after infusion and 0.994, 0.993, and 0.919 after oral administration. Despite the good correlation observed, there was little confidence in these results due to limited data available for a linear regression analysis. Accordingly, an analysis of variance (ANOVA) (6) was performed on the area under the curve divided by the administered dose, with the total data available, obtained after either intravenous or oral administration. It failed to show a significant difference at the 5% level between the administered doses (${}_{16}{}^{3}F = 0.46$), route of drug administration (${}_{16}{}^{1}F = 0.02$), and among the subjects (${}_{16}{}^{2}F = 0.68$). Similarly, the same ANOVA failed to show any difference between administered doses (${}_{16}{}^{3}F = 0.51$) and dosage forms (${}_{16}{}^{1}F = 0.26$) when considering urinary unchanged pefloxacin percentages. For this parameter, the analysis showed significant differences among individuals ($p < 0.05$).

Therefore, from all statistical calculations performed, it can be concluded that, within the range of the doses administered, the pharmacokinetic parameters of pefloxacin are not sensitive to dose variations. This includes both systemic and presystemic drug elimination because dose independency is observed after both intravenous and oral administration. The availability of the tablet form can be expected to be complete.

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